Amendments to the Specification:

Please replace the paragraph at page 1, lines 4-17, with the following amended paragraph:

This application is a continuation-in-part of U.S. Serial No. 10/399,213, filed April 14, 2003 (abandoned), which is a national phase filing of PCT AU01/01291, filed October 15, 2001, which is a PCT filing of AU provisional application PR0745, filed October 13, 2000. This application is also a continuation-in-part of U.S. Serial No. 60/527001, filed December 5, 2003. This application is also a continuation-in-part of U.S. Serial No. 10/419,068 filed April 18, 2003 (abandoned), which is a continuation-in-part of U.S. Serial No. 09/976,712 filed October 12, 2001 (abandoned), which is a continuation-in-part of U.S. Serial No. 09/969,510 (abandoned), which is a continuation-in-part of U.S. Serial No. 09/966,576 filed September 26, 2001 (abandoned), which is a continuation-in-part of U.S. Serial No. 09/758,910, filed January 10, 2001 (abandoned), which is a continuation-in-part of U.S. Serial No. 09/795,286, filed October 13, 2000 (abandoned), which is a continuation-in-part of AU Provisional Application PR0745, filed October 13, 2000, and of U.S. Serial No. 09/795,302, filed October 13, 2000 (abandoned), which is a continuation-in-part of PCT AU00/00329, filed April 17, 2000, which is a PCT filing of AU provisional application PP9778 filed April 15, 1999. Each of these applications is hereby incorporated by reference.

Please replace the paragraph bridging pages 1 and 2, with the following amended paragraph:

The major function of the immune system is to distinguish "foreign" (that is derived from any source outside the body) antigens from "self" (that is derived from within the body) and respond accordingly to protect the body against infection. In more practical terms, the immune response has also been described as responding to "danger" signals. These "danger" signals may be any change in the property of a cell or tissue which alerts cells of the immune system that this cell/tissue in question is no longer "normal." Such alterations may be very important in causing, for example, rejection of tumors. However, this "danger" signal may also

be the reason why some autoimmune diseases start, due to either inappropriate cell changes in the "self" cells targeted by the immune system (*e.g.*, the ~~□-islet~~ β-islet cells targeted in Diabetes mellitus), or inappropriate cell changes in the immune cells themselves, leading these cells to target normal "self" cells. In normal immune responses, the sequence of events involves dedicated antigen presenting cells (APC) capturing foreign antigen and processing it into small peptide fragments which are then presented in clefts of major histocompatibility complex (MHC) molecules on the APC surface. The MHC molecules can either be of class I expressed on all nucleated cells (recognized by cytotoxic T cells (Tc)) or of class II expressed primarily by cells of the immune system (recognized by helper T cells (Th)). Th cells recognize the MHC II/peptide complexes on APC and respond; factors released by these cells then promote the activation of either of both Tc cells or the antibody producing B cells which are specific for the particular antigen. The importance of Th cells in virtually all immune responses is best illustrated in HIV/AIDS where their absence through destruction by the virus causes severe immune deficiency eventually leading to death. Inappropriate development of Th (and to a lesser extent Tc) can lead to a variety of other diseases such as allergies, cancer and autoimmunity.

Please replace the paragraph on page 3, lines 20-31, with the following amended paragraph:

The thymus is arguably the major organ in the immune system because it is the primary site of production of T lymphocytes. Its role is to attract appropriate bone marrow-derived precursor cells from the blood, and induce their commitment to the T cell lineage including the gene rearrangements necessary for the production of the T cell receptor for antigen (TCR). Associated with this is a remarkable degree of cell division to expand the number of T cells and hence ~~increase~~ increases the likelihood that every foreign antigen will be recognized and eliminated. A unique feature of T cell recognition of antigen, however, is that unlike B cells, the TCR only recognizes peptide fragments physically associated with MHC molecules; normally this is self MHC and this ability is selected for in the thymus. This process is called positive

selection and is an exclusive feature of cortical epithelial cells. If the TCR fails to bind to the self MHC/peptide complexes, the T cell dies by "neglect" – it needs some degree of signalling through the TCR for its continued maturation.

Please replace the paragraph on page 7, lines 7-13, with the following amended paragraph:

The present inventors have demonstrated that thymic atrophy (~~aged induced~~ age-induced, or as a consequence of conditions such as chemotherapy or radiotherapy) can be profoundly reversed by inhibition of sex steroid production, with virtually complete restoration of thymic structure and function. The present inventors have also found that the basis for this thymus regeneration is in part due to the initial expansion of precursor ~~cells which~~ cells, which are derived both intrathymically and via the blood stream. This finding suggests that is possible to seed the thymus with exogenous haemopoietic stem cells ~~(HSC) which~~ (HSC), which have been injected into the subject.

Please replace the paragraph on page 7, lines 14-18, with the following amended paragraph:

The ability to seed the thymus with genetically modified or exogenous HSC by disrupting sex ~~steroid signalling~~ steroid-signaling to the thymus, means that gene therapy in the HSC may be used more efficiently to treat T cell (and myeloid cells which develop in the thymus) disorders. HSC stem cell therapy has met with little or no success to date because the thymus is dormant and incapable of taking up many if any HSC, with T cell production less than 1% of normal levels.

Please replace the paragraph on page 8, lines 12-17, with the following amended paragraph:

In one aspect the present disclosure provides a method of gene therapy, the method comprising disrupting sex ~~steroid-mediated~~ steroid-mediated signaling to the thymus in the patient. In one embodiment, GnRH analogs (agonist and antagonists thereto) are used to disrupt sex steroid-mediated signaling to the thymus. In another embodiment, GnRH analogs directly stimulate (*i.e.*, directly increase the functional activity of) the thymus, bone marrow, and pre-existing cells of the immune system, such as T cells, B cells, and dendritic cells (DC).

Please replace the paragraph on page 8, lines 18-20, with the following amended paragraph:

In one aspect the present disclosure provides a method for treating a T cell disorder in a patient, the method comprising disrupting sex ~~steroid-mediated~~ steroid-mediated signaling to the thymus in the patient and transplanting into the patient bone marrow or HSC.

Please replace the paragraph on page 9, lines 3-9, with the following amended paragraph:

In certain embodiments, inhibition of sex steroid production is achieved by either castration or administration of a sex steroid ~~analogue(s)~~ analogs. Non-limiting sex steroid ~~analogues~~ analogs include eulexin, goserelin, leuprolide, dioxalan derivatives such as triptorelin, meterelin, buserelin, histrelin, nafarelin, lutrelin, leuprorelin, and luteinizing hormone-releasing hormone ~~analogues~~ analogs. In some embodiments, the sex steroid ~~analogue~~ analog is an ~~analogue~~ analog of luteinizing hormone-releasing hormone. In certain embodiments, the luteinizing hormone-releasing hormone ~~analogue~~ analog is deslorelin.

Please replace the paragraph bridging pages 9 and 10, with the following amended paragraph:

In another aspect, the present disclosure provides for the reactivation of the thymus by disrupting sex ~~steroid mediated~~ steroid-mediated signaling. In one embodiment, castration is used to disrupt the sex ~~steroid mediated~~ steroid-mediated signaling. In one embodiment chemical castration is used. In another embodiment surgical castration is used. Castration reverses the state of the thymus to its pre-pubertal state, thereby reactivating it. Both of these processes result in a loss of sex steroids; they may also induce increases in other molecules which increase immune responsiveness.

Please replace the paragraph on page 10, lines 4-7, with the following amended paragraph:

In a particular embodiment sex ~~steroid mediated~~ steroid-mediated signaling to the thymus is blocked by the administration of agonists or antagonists of LHRH, anti-estrogen antibodies, anti-androgen antibodies, or passive (antibody) or active (antigen) anti-LHRH vaccinations, or combinations thereof ("blockers").

Please replace the paragraph on page 10, lines 16-22, with the following amended paragraph:

In cases where the subject is infected with HIV, the HSC may be genetically modified such that they and their progeny, in particular T cells, macrophages and dendritic cells, are resistant to infection ~~and / or~~ and/or destruction with the HIV virus. The genetic modification may involve introduction into the HSC of one or more nucleic acid molecules which prevent viral replication, assembly and/or infection. The nucleic acid molecule may be a gene which ~~enclodes~~ encodes an antiviral protein, an antisense construct, a ribozyme, a dsRNA and a catalytic nucleic acid molecule.

Please replace the paragraph bridging pages 28 and 29, with the following amended paragraph:

Examples of infectious viruses include: Retroviridae (*e.g.*, human immunodeficiency viruses, such as HIV-1 (also referred to as HTLV-III, LAV or HTLV-III/LAV), or HIV-III; and other isolates, such as HIV-LP; Picornaviridae (*e.g.*, polio viruses, hepatitis A virus; enteroviruses, human coxsackie viruses, rhinoviruses, echoviruses); Calciviridae (*e.g.*, strains that cause gastroenteritis); Togaviridae (*e.g.*, equine encephalitis viruses, rubella viruses); Flaviridae (*e.g.*, dengue viruses, encephalitis viruses, yellow fever viruses); Coronaviridae (*e.g.*, coronaviruses, severe acute respiratory syndrome (SARS) virus); Rhabdoviridae (*e.g.*, vesicular stomatitis viruses, rabies viruses); Filoviridae (*e.g.*, ebola viruses); Paramyxoviridae (*e.g.*, parainfluenza viruses, mumps virus, measles virus, respiratory syncytial virus); Orthomyxoviridae (*e.g.*, influenza viruses); Bungaviridae (*e.g.*, Hantaan viruses, bunga viruses, phleboviruses and Nairo viruses); ~~Arena viridae~~ Arenaviridae (hemorrhagic fever viruses); Reoviridae (*e.g.*, reoviruses, orbiviurses and rotaviruses); Birnaviridae; Hepadnaviridae (*e.g*, Hepatitis B virus); Parvoviridae (parvoviruses); Papovaviridae (papilloma viruses, polyoma viruses); Adenoviridae (most adenoviruses); Herpesviridae (*e.g.*, herpes simplex virus (HSV) 1 and 2, varicella zoster virus, cytomegalovirus (CMV), herpes viruses); Poxviridae (*e.g.*, variola viruses, vaccinia viruses, pox viruses); and Iridoviridae (*e.g.*, African swine fever virus); and unclassified viruses (*e.g.*, the etiological agents of Spongiform encephalopathies, the agent of delta hepatities (thought to be a defective satellite of hepatitis B virus), the agents of non-A, non-B hepatitis (class 1=internally transmitted; class 2=parenterally transmitted (*i.e.*, Hepatitis C); Norwalk and related viruses, and astroviruses).

Please replace the paragraph on page 29, lines 4-14, with the following amended paragraph:

Examples of infectious bacteria include: ~~*Helicobacter pyloris*~~ *Helicobacter pylori*, *Borelia burgdorferi*, *Legionella pneumophilia*, *Mycobacteria* sporozoites (sp.) (*e.g. M. tuberculosis, M. avium,*

M. intracellulare, M. kansaii, M. gordonae), *Staphylococcus aureus, Neisseria gonorrhoeae, Neisseria meningitidis, Listeria monocytogenes, Streptococcus pyogenes* (Group A Streptococcus), *Streptococcus agalactiae* (Group B Streptococcus), *Streptococcus* (viridans group), *Streptococcus faecalis, Streptococcus bovis, Streptococcus* (anaerobic sps.), *Streptococcus pneumoniae,* pathogenic *Campylobacter* sp., *Enterococcus* sp., *Haemophilus influenzae, ~~Bacillus antracis~~ Bacillus anthracis, Corynebacterium diphtheriae, Corynebacterium* sp., *Erysipelothrix rhusiopathiae, Clostridium perfringens, Clostridium tetani, Enterobacter aerogenes, Klebsiella pneumoniae, Pasturella multocida, Bacteroides* sp., *Fusobacterium nucleatum, Streptobacillus moniliformis, Treponema pallidium, Treponema pertenue, Leptospira,* and *Actinomyces israelli.*

Please replace the paragraph on page 30, lines 9-14, with the following amended paragraph:

Methods of detecting new T cells in the blood are known in the art. For instance, one method of T cell detection is by determining the existence of T cell receptor excision circles (TREC's), which are formed when the TCR is being formed and are lost in the cell after it divides. Hence, TREC's are only found in new (naïve) T cells. TREC levels are one indicator of thymic function in humans. These and other methods are described in detail in ~~WO/ 00 230,256~~ WO 02/030256, which is herein incorporated by reference.

Please replace the paragraph bridging pages 33 and 34, with the following amended paragraph:

Administration may be by any method which delivers the sex ~~steroid ablating~~ steroid-ablating agent into the body. Thus, the sex ~~steroid ablating~~ steroid-ablating agent ~~maybe be~~ may be administered, in accordance with the invention, by any route including, without limitation, intravenous, subdermal, subcutaneous, intramuscular, topical, and oral routes of administration. One non-limiting example of administration of a sex ~~steroid ablating~~ steroid-ablating agent is a subcutaneous/intradermal injection of a "slow-release" depot of GnRH

agonist (*e.g.*, one, three, or four month ~~Lupron®~~ LUPRON® injections) or a subcutaneous/intradermal injection of a "slow-release" GnRH-containing implant (*e.g.*, one or three month ~~Zoladex®~~ ZOLADEX®, *e.g.*, 3.6 mg or 10.8 mg implant). These could also be given ~~intramuscular~~ intramuscularly (i.m.), intravenously (i.v.) or orally, depending on the appropriate formulation. Another example is by subcutaneous injection of a "depot" or "impregnated implant" containing, for example, about 30 mg of ~~Lupron®~~ LUPRON® ~~(e.g., Lupron Depot®,(leuprolide acetate for depot suspension) TAP Pharmaceuticals Products, Inc., Lake Forest, IL)~~ (*e.g.*, LUPRON DEPOT®, (leuprolide acetate for depot suspension) TAP Pharmaceutical Products, Inc., Lake Forest, IL). A 30 mg ~~Lupron®~~ LUPRON® injection is sufficient for four months of sex steroid ablation to allow the thymus to rejuvenate and export new naïve T cells into the blood stream.

Please replace the paragraph at page 34, lines 5-29, with the following amended paragraph:

In some embodiments, sex steroid ablation or inhibition of sex ~~steroid signaling~~ steroid-signaling is accomplished by administering an anti-androgen such as an androgen blocker (*e.g.*, bicalutamide, trade names ~~Cosudex® or Casodex®~~ COSUDEX® or CASODEX®, AstraZeneca, ~~Aukland~~ Auckland, NZ), either alone or in combination with an LHRH analog or any other method of castration. Sex steroid ablation or interruption of sex ~~steroid signaling~~ steroid-signaling may also be accomplished by administering cyproterone acetate (trade name, ~~Androcor®~~ ANDROCOR®, ~~Shering~~ Schering AG, Germany; *e.g.*, 10-1000 mg, 100 mg bd or tds, or 300 mg IM weekly, a 17-hydroxyprogesterone acetate, which acts as a progestin, either alone or in combination with an LHRH analog or any other method of castration. Alternatively, other anti-androgens may be used (*e.g.*, antifungal agents of the imidazole class, such as ~~liarozole(Liazol® e.g., 150 mg/day, an aromatase inhibitor)~~ liarozole (~~Liazol®~~ LIAZOL®, *e.g.*, 150 mg/day, an aromatase inhibitor) and ketoconazole, bicalutamide (trade name ~~Cosudex® or Casodex®~~ COSUDEX® or CASODEX®, 5-500 mg, *e.g.*, 50 mg po QID), flutamide (trade names

~~Euflex® and Eulexin®,~~ EUFLEX® and EULEXIN®, ~~Shering~~ Schering Plough Corp, N.J.; 50-500 mg *e.g.*, 250 or 750 po QID), megestrol acetate (~~Megace®~~ MEGACE®) *e.g.*, 480-840 mg/day or nilutamide (trade names ~~Anandron®, and Nilandron®,~~ ANANDRON®, and NILANDRON®, Roussel, France *e.g.*, orally, 150-300 mg/day)). Antiandrogens are often important in therapy, since they are commonly utilized to address flare by GnRH analogs. Some antiandrogens act by inhibiting androgen receptor translocation, which interrupts negative feedback resulting in increased testosterone levels and minimal loss of libido/potency. Another class of anti-androgens useful in the present invention are the selective androgen receptor modulators (SARMS) (*e.g.*, quinoline derivatives, bicalutamide (trade name ~~Cosudex® or Casodex®~~ COSUDEX® or CASODEX®,, ICI Pharmaceuticals, England *e.g.*, orally, 50 mg/day), and flutamide (trade name ~~Eulexin®,~~ EULEXIN®, *e.g.*, orally, 250 mg/day)). Other well known anti-androgens include 5 alpha reductase inhibitors (*e.g.*, ~~dutasteride,(e.g., 0.5 mg/day)~~ dutasteride, (*e.g.*, 0.5 mg/day) which inhibits both 5 alpha reductase isoenzymes and results in greater and more rapid DHT suppression; finasteride (trade name ~~Proscar®;~~ PROSCAR®; ~~0.5-500mg e.g.,~~ 0.5-500 mg, e.g., 5 mg po daily), which inhibits ~~5alpha~~ 5 alpha reductase 2 and consequent DHT production, but has little or no effect on testosterone or ~~LH levels);~~ LH levels).

Please replace the paragraph at page 35, lines 1-22, with the following amended paragraph:

In other embodiments, sex steroid ablation or inhibition of sex ~~steroid signaling~~ steroid-signaling is accomplished by administering anti-estrogens either alone or in combination with an LHRH analog or any other method of castration. Some anti-estrogens (*e.g.*, anastrozole (trade name ~~Arimidex®~~ ARIMIDEX®), and fulvestrant (trade name ~~Faslodex®~~ FASLODEX®) act by binding the estrogen receptor (ER) with high affinity similar to estradiol and consequently inhibiting estrogen from binding. ~~Faslodex®~~ FASLODEX® binding also triggers conformational change to the receptor and down-regulation of estrogen receptors, without significant change in FSH or LH levels. Other non-limiting examples of anti-estrogens are

tamoxifen (trade name ~~Nolvadex®~~ NOLVADEX®); ~~Clomiphene (trade name Clomid®) *e.g.*, 50-250mg/day~~ Clomiphene (trade name CLOMID®) *e.g.*, 50-250 mg/day, a non-steroidal ER ligand with mixed agonist/antagonist properties, which stimulates release of gonadotrophins; Fulvestrant (trade name ~~Faslodex®~~ FASLODEX®; ~~10-1000mg~~ 10-1000 mg, *e.g.*, ~~250mg~~ 250 mg IM monthly); diethylstilbestrol ((DES), trade name ~~Stilphostrol®~~ STILPHOSTROL®) ~~*e.g.*, 1-3mg/day~~ *e.g.*, 1-3 mg/day, which shows estrogenic activity similar to, but greater than, that of estrone, and is therefore considered an estrogen agonist, but binds both androgen and estrogen receptors to induce feedback inhibition on FSH and LH production by the pituitary, diethylstilbestrol diphosphate ~~*e.g.*, 50 to 200 mg/day~~ *e.g.*, 50 to 200 mg/day; as well as ~~danazol, droloxifene~~ danazol, droloxifene, and iodoxyfene, which each act as antagonists. Another class of anti-estrogens which may be used either alone or in combination with other methods of castration, are the selective estrogen receptor modulators (SERMS) (*e.g.*, toremifene (trade name ~~Fareston®,~~ FARESTON®, ~~5-1000mg~~ 5-1000 mg, *e.g.*, ~~60mg~~ 60 mg po QID), raloxofene (trade name ~~Evista®~~ EVISTA®), and tamoxifen (trade name ~~Nolvadex®,~~ NOLVADEX®, ~~1-1000mg~~ 1-1000 mg, *e.g.*, ~~20mg~~ 20 mg po bd), which behaves as an agonist at estrogen receptors in bone and the cardiovascular system, and as an antagonist at estrogen receptors in the mammary gland). Estrogen receptor downregulators (ERDs) (*e.g.*, tamoxifen (trade name, ~~Nolvadex®,~~ NOLVADEX®)) may also be used in the present invention.

Please replace the paragraph bridging pages 35 and 36, with the following amended paragraph:

Other non-limiting examples of methods of inhibiting ~~sex steroid signalling~~ sex steroid-signaling which may be used either alone or in combination with other methods of castration, include aromatase inhibitors and other adrenal gland blockers (*e.g.*, Aminoglutethimide, formestane, vorazole, exemestane, anastrozole (trade name ~~Arimidex®,~~ ARIMIDEX®, ~~0.1-100mg~~ 0.1-100 mg, *e.g.*, 1 mg po QID), which lowers estradiol and increases LH and testosterone), letrozole (trade name Femara®, 0.2-500 mg, *e.g.*, ~~2.5mg~~ 2.5 mg po QID), and

exemestane ~~(trade name Aromasin®)1-2000mg, *e.g.*, 25mg/day)~~ (trade name AROMASIN®) 1-2000 mg, *e.g.*, 25 mg/day); aldosterone antagonists (*e.g.*, spironolactone (trade name, ~~Aldactone®~~ ALDACTONE®)*e.g.*, ~~100 to 400mg/day~~ 100 to 400 mg/day), which blocks the androgen cytochrome P-450 receptor;) and eplerenone, a selective aldosterone-receptor antagonist) antiprogestogens (*e.g.*, medroxypregesterone acetate, ~~*e.g.*5mg/day~~ *e.g.*, 5 mg/day, which inhibits testosterone syntheses and LH synthesis); and progestins and anti-progestins such as the selective progesterone response modulators (SPRM) (*e.g.*, megestrol acetate ~~*e.g.*,160mg/day~~ *e.g.*, 160 mg/day, mifepristone (RU 486, ~~Mifeprex®,~~ MIFEPREX®, ~~*e.g.*200mg/day~~ *e.g.*, 200 mg/day); and other compounds with estrogen/antiestrogenic activity, (*e.g.*, phytoestrogens, flavones, isoflavones and coumestan derivatives, lignans, and industrial compounds with phenolic ring (*e.g.*, DDT)). Also, anti-GnRH vaccines (see, *e.g.*, Hsu *et al.*, (2000) *Cancer Res.* 60:3701; Talwar, (1999) *Immunol. Rev.* 171:173-92), or any other pharmaceutical which mimics the effects produced by the aforementioned drugs, may also be used. In addition, steroid receptor based modulators, which may be targeted to be thymic specific, may also be developed and used. Many of these mechanisms of inhibiting sex ~~steroid signaling~~ steroid-signaling are well known. Each ~~drugs~~ drug may also be used in modified form, such as acetates, citrates and other salts thereof, which are well known to those in the art.

Please replace the paragraph on page 36, lines 14-19, with the following amended paragraph:

Because of the complex and interwoven feedback mechanisms of the hormonal system, administration of sex steroids may result in inhibition of sex ~~steroid signalling~~ steroid-signaling. For example, estradiol decreases gonadotropin production and sensitivity to GnRH action. However, higher levels of estradiol result in gonadotropin surge. Likewise, progesterone influences frequency and amount of LH release. In men, testosterone inhibits gonadotropin production. Estrogen administered to men decreases LH and testosterone, and anti-estrogen increases LH.

Please replace the paragraph on page 36, lines 24-28, with the following amended paragraph:

In some embodiments, the sex ~~steroid-mediated~~ steroid-mediated signaling to the thymus is disrupted by administration of gonadotrophin-releasing hormone (GnRH) or an analog thereof. GnRH is a hypothalamic decapeptide that stimulates the secretion of the pituitary gonadotropins, leutinizing hormone (LH) and follicle-stimulating hormone (FSH). Thus, GnRH, *e.g.*, in the form of Synarel or Lupron, will suppress the pituitary gland and stop the production of FSH and LH.

Please replace the paragraph bridging pages 37 and 38, with the following amended paragraph:

In some embodiments, the sex ~~steroid-mediated~~ steroid-mediated signaling to the thymus is disrupted by administration of a sex steroid analog, such as an analog of leutinizing hormone-releasing hormone (LHRH). ~~Sex steroid analogs and their use in therapies and chemical castration are well known.~~ Sex steroid analogs are commercially known and their use in therapies and chemical castration are well known. Such analogs include, but are not limited to, the following agonists of the LHRH receptor (LHRH-R): buserelin (*e.g.*, buserelin acetate, trade names ~~Suprefact®~~ SUPREFACT® (*e.g.*, 0.5-02 mg s.c./day), ~~Suprefact Depot®,~~ SUPREFACT DEPOT®, and ~~Suprefact®~~ SUPREFACT® Nasal Spray (*e.g.*, 2 μg per nostril, every 8 hrs.), Hoechst, also described in U.S. Patent Nos. 4,003,884, 4,118,483, and 4,275,001); ~~Cystorelin®~~ CYSTORELIN® (*e.g.*, gonadorelin diacetate tetrahydrate, Hoechst); deslorelin (*e.g.*, ~~desorelin~~ deslorelin acetate, ~~Deslorell®,~~ DESLORELL®, Balance Pharmaceuticals); gonadorelin (*e.g.*, gonadorelin hydrocholoride, trade name ~~Factrel®~~ FACTREL® (100 μg i.v. or s.c.), Ayerst Laboratories); goserelin (goserelin acetate, trade name ~~Zoladex®,~~ ZOLADEX®, AstraZeneca, ~~Aukland~~ Auckland, NZ, also described in U.S. Patent Nos. 4,100,274 and 4,128,638; GB 9112859 and GB 9112825); histrelin (*e.g.*, ~~histerelin acetate~~ histrelin acetate, ~~Supprelin®,~~ SUPPRELIN®, (~~s.c., 10 μg/kg.day~~ s.c., 10 μg/kg/day), Ortho, also described in EP 217659); leuprolide (leuprolide

acetate, trade name ~~Lupron® or Lupron Depot®;~~ LUPRON® or LUPRON DEPOT®; Abbott/TAP, Lake Forest, IL, also described in U.S. Patent Nos. ~~4,490,291 3,972,859~~, 4,490,291, 3,972,859, 4008,209, 4,992,421, and 4,005,063; DE 2509783); leuprorelin (*e.g.*, ~~leuproelin~~ leuprorelin acetate, trade name ~~Prostap SR®~~ PROSTAP SR® (*e.g.*, single 3.75 mg dose s.c. or i.m./month), ~~Prostap3®~~ PROSTAP3® (*e.g.*, single ~~11.25mg~~ 11.25 mg dose s.c. every 3 months), Wyeth, USA, also described in Plosker *et al.*, (1994) Drugs 48:930); lutrelin (Wyeth, USA, also described in U.S. Patent No. 4,089,946); ~~Meterelin®~~ METERELIN® (*e.g.*, Avorelina (*e.g.*, 10-15 mg slow-release formulation), also described in ~~EP 23904 and~~ WO 91/18016); nafarelin (*e.g.*, trade name ~~Synarel®~~ SYNAREL® (i.n. 200-1800 μg/day), Syntex, also described in U.S. Patent No. 4,234,571; ~~W0 93/15722~~ WO 93/15722; and ~~EP 52510~~ EP0052510); and triptorelin (*e.g.*, triptorelin pamoate; trade names ~~Trelstar LA®~~ TRELSTAR LA® (11.25 mg over 3 months), ~~Trelstar LA Debioclip®~~ TRELSTAR LA DEBIOCLIP® (pre-filled, single dose delivery), ~~LA Trelstar Depot®~~ LA TRELSTAR DEPOT® (3.75 mg over one month), and ~~Decapeptyl®,~~ DECAPEPTYL®, Debiopharm S.A., ~~Switserland~~ Switzerland, also described in U.S. Patent Nos. 4,010,125, 4,018,726, 4,024,121, and 5,258,492; EP 364819). LHRH analogs also include, but are not limited to, the following antagonists of the LHRH-R: abarelix (trade name ~~Plenaxis™~~ PLENAXIS™ (*e.g.*, 100 mg i.m. on days 1, 15 and 29, then every 4 weeks thereafter), Praecis Pharmaceuticals, Inc., Cambridge, MA) and cetrorelix (*e.g.*, cetrorelix acetate, trade name ~~Cetrotide™~~ CETROTIDE™ (*e.g.*, 0.25 or 3 mg s.c.), Zentaris, Frankfurt, Germany). Additional sex steroid analogs include ~~Eulexin®~~ EULEXIN® (*e.g.*, flutamide (*e.g.*, 2 capsules 2x/day, total 750 mg/day), Schering-Plough Corp., also described in FR 7923545, WO 86/01105 and PT 100899), and dioxane derivatives ~~(*e.g.*, those described in EP 413209),~~ and other LHRH ~~analogues~~ analogs such as are described in EP 181236, U.S. Patent Nos. 4,608,251, 4,656,247, 4,642,332, 4,010,149, 3,992,365, and 4,010,149. Combinations of agonists, combinations of antagonists, and combinations of agonists and antagonists are also included. One non-limiting analog of the invention is deslorelin (described in U.S. Patent No. 4,218,439). For a more extensive ~~list, of~~ list of analogs, see Vickery *et al.* (1984) LHRH and Its Analogs: Contraceptive & Therapeutic Applications (Vickery *et al.*, eds.) MTP Press Ltd., Lancaster, PA. Each analog may

also be used in modified form, such as acetates, citrates and other salts thereof, which are well known to those in the art.

Please replace the paragraph bridging pages 41 and 42, with the following amended paragraph:

The intracellular receptors are members of the nuclear receptor superfamily. They are located in the cytoplasm of the cell and are transported to the nucleus after binding with the sex steroid hormone where they alter the transcription of specific genes. Receptors for the sex steroid hormones exist in several forms. Well known in the literature are two forms of the progesterone receptor, PRA and PRB, and three forms of the estrogen receptor, ERα, ERβ1 and ERβ2. Transcription of genes in response to the binding of the sex steroid hormone receptor to the steroid response element in the promoter region of the gene can be modified in a number of ways. Co-activators and co-repressors exist within the nucleus of the target cell that can modify binding of the steroid-receptor complex to the DNA and thereby effect transcription. The identity of many of these co-activators and co-repressors are known and methods of modifying their actions on steroid receptors are the topic of current research. Examples of the transcription factors involved in sex steroid hormone action are NF-1, SP1, ~~Oct-1and~~ Oct-1 and TFIID. These co-regulators are required for the full action of the steroids. Methods of modifying the actions of these nuclear regulators could involve the balance between activator and repressor by the use of antagonists or through control of expression of the genes encoding the regulators.

Please replace the paragraph at page 47, lines 14-18, with the following amended paragraph:

_____Those skilled in the art would be able to develop suitable anti-HIV constructs for use in the present invention. Indeed, a number of anti-HIV antisense constructs and ribozymes have already been developed and are described, for example; in U.S. Patent No. 5,811,275, U.S. Patent

No. 5,741,706, PCT Publication No. WO 94/26877, Australian Patent Application No. 56394/94 and U.S. Patent No. 5,144,019.

Please replace the paragraph at page 61, lines 15-20, with the following amended paragraph:

Animals. CBA/CAH and C57Bl6/J male mice were obtained from Central Animal Services, Monash University and were housed under conventional conditions. C57Bl6/J Ly5.1$^+$ were obtained from the ~~Central Animal Services Monash University~~ Central Animal Services, Monash University, the ~~Walterand~~ Walter and Eliza Hall Institute for Medical Research (Parkville, Victoria) and the A.R.C. (Perth Western Australia) and were housed under conventional conditions. Ages ranged from 4-6 weeks to 26 months of age and are indicated where relevant.

Please replace the paragraph at page 66, lines 17-24, with the following amended paragraph:

The DN subpopulation, in addition to the thymocyte precursors, contains ~~(αβTCR$^+$CD4$^-$CD8$^-$~~ αβTCR$^+$CD4$^-$CD8$^-$ thymocytes, which are thought to have downregulated both co-receptors at the transition to SP cells (Godfrey & Zlotnik, 1993). By gating on these mature cells, it was possible to analyze the true TN compartment (CD3$^-$CD4$^-$CD8$^-$) and their subpopulations expressing CD44 and CD25. Figures 5H, 5I, 5J, and 5K illustrate the extent of proliferation within each subset of TN cells in young, old and castrated mice. This showed a significant ($p<0.001$) decrease in proliferation of the TN1 subset (CD44$^+$CD25$^-$ CD3$^-$CD4$^-$CD8$^-$), from ~~10%%~~ 10% in the normal young to around 2% at 18 months of age (Fig. 5H) which was restored by 1 week post-castration.

Please replace the paragraph bridging pages 74 and 75, with the following amended paragraph:

The above findings indicate a defect in the thymic epithelium ~~rendering it~~ rendering it incapable of providing the developing thymocytes with the necessary stimulus ~~for, development~~ for development. However, the symbiotic nature of the ~~thymic, epithelium~~ thymic epithelium and thymocytes makes it difficult to ascertain the exact pathway of destruction by the sex steroid influences. The medullary epithelium requires cortical T cells for its proper development and maintenance. Thus, if this population is ~~diminished, .the~~ diminished, the medullary thymocytes may not receive adequate signals for development. This particularly seems to affect the $CD8^+$ population. $IRF^{-/-}$ mice show a decreased number of $CD8^+$ T cells. It would therefore, be interesting to determine the proliferative capacity of these cells.

Please replace the paragraph at page 84, lines 13-26, with the following amended paragraph:

In noncastrated mice, there was a profound decrease in thymocyte number over the 4 week time period, with little or no evidence of regeneration (Fig. 21A). In the castrated group, however, by two weeks there was already extensive thymopoiesis which by four weeks had returned to control levels, being 10 fold higher than in noncastrated mice. Flow cytometeric analysis of the thymii with respect to CD45.2 (donor-derived antigen) demonstrated that no ~~donor derived~~ donor-derived cells were detectable in the noncastrated group at 4 weeks, but remarkably, virtually all the thymocytes in the castrated mice were donor-derived at this time point (Fig. 21B). Given this extensive enhancement of thymopoiesis from donor-derived haemopoietic precursors, it was important to determine whether T cell differentiation had proceeded normally. CD4, CD8 and TCR defined subsets were ~~analysed~~ analyzed by flow cytometry. There were no proportional differences in thymocytes subset proportions 2 weeks after reconstitution (Fig. 22). This observation was not possible at 4 weeks, because the

noncastrated mice were not reconstituted with donor-derived cells. However, at this time point the thymocyte proportions in castrated mice appear normal.

Please replace the paragraph bridging pages 89 and 90, with the following amended paragraph:

The patient was given sex steroid ablation therapy in the form of delivery of an LHRH agonist. This was given in the form of either Leucrin (depot injection; ~~22.5mg~~ 22.5 mg) or Zoladex (implant; 10.8 mg), either one as a single dose effective for 3 months. This was effective in reducing sex steroid levels sufficiently to reactivate the thymus. In other words, the serum levels of sex steroids were undetectable (castrate; ~~<0.5ng/ml~~ <0.5 ng/ml blood). In some cases it is also necessary to deliver a suppresser of adrenal gland production of sex steroids. Cosudex (~~5mg/day~~ 5 mg/day) may be delivered as one tablet per day for the duration of the sex steroid ablation therapy. Adrenal gland production of sex steroids makes up around 10-15% of a human's steroids.

Please replace the paragraph at page 90, lines 3-8, with the following amended paragraph:

Reduction of sex steroids in the blood to minimal values took about 1-3 weeks; concordant with this was the reactivation of the thymus. In some cases it is necessary to extend the treatment to a second 3 month injection/implant. The thymic expansion may be increased by simultaneous enhancement of blood HSC either as an allogeneic donor (in the case of grafts of foreign tissue) or autologous HSC (by injecting the host with G-CSF to mobilize these HSC from the bone marrow to the ~~thymus~~ thymus).

Please replace the paragraph at page 91, lines 13-29, with the following amended paragraph:

Where practical, the level of hematopoietic stem cells (HSC) in the donor blood is enhanced by injecting into the donor granulocyte-colony stimulating factor (G-CSF) at ~~10μg/kg~~ 10 μg/kg for 2-5 days prior to cell collection (*e.g.*, one or two injections of 10 μg/kg per day for each of 2-5 days). $CD34^+$ donor cells are purified from the donor blood or bone marrow, such as by using a flow cytometer or immunomagnetic beading. Antibodies that specifically bind to human CD34 are commercially available (from, *e.g.*, Research Diagnostics Inc., Flanders, NJ). Donor-derived HSC are identified by flow cytometry as being $CD34^+$. These ~~CD34+~~ $CD34^+$ HSC may also be expanded by in vitro culture using feeder cells (*e.g.*, fibroblasts), growth factors such as stem cell factor (SCF), and LIF to prevent differentiation into specific cell types. At approximately 3-4 weeks post LHRH agonist delivery (*i.e.*, just before or at the time the thymus begins to regenerate) the patient is injected with the donor HSC, optimally at a dose of about 2-4 x 10^6 cells/kg. G-CSF may also be injected into the recipient to assist in expansion of the donor HSC. If this timing schedule is not possible because of the critical nature of clinical condition, the HSC could be administered at the same time as the GnRH. It may be necessary to give a second dose of HSC 2-3 weeks later to assist in the thymic regrowth and the development of donor DC (particularly in the thymus). Once the HSC have ~~engraftment~~ engrafted (*i.e.*, have incorporated into the bone marrow and thymus), the effects should be permanent since the HSC are self-renewing.

Please replace the paragraph bridging pages 92 and 93, with the following amended paragraph:

Influenza viruses are segmented RNA viruses that cause highly contagious acute respiratory infections. These viruses are endemic in man, where they are particularly devastating for the very young and the very old. The major problem associated with vaccine development against influenza is that these viruses have the ability to escape immune

surveillance and remain in a host population. This escape is associated with changes in antigenic sites on the hemagglutinin (HA) and neuraminidase (N) envelope glycoproteins by phenomena termed antigenic drift and antigenic shift. Antigenic drift occurs when a subtype of an influenza virus H (for example H3) is selected for antigenic determinants that are not recognized by the anti-H3 antibody present in a population. This allows the virus to superinfect individuals who have already been infected by an H3 virus. Antigenic shift occurs when the influenza virus segmented genome reassorts to acquire an H belonging to another subtype (for example H2 instead of H3). The primary correlate for protection against influenza virus is neutralizing antibody against HA protein that undergoes strong selection for antigenic drift and shift. However, much more conserved antigenic cross-reactivities for different strains of influenza virus occur between internal proteins, such as the nucleoprotein (NP) (Shu, Bean and Webster, 1993). CTL and protection from influenza challenge following immunization with a polynucleotide encoding NP has previously been shown (*Science* 259:1745 ~~(1993)~~ (1993)).

Please replace the paragraph bridging pages 95 and 96, with the following amended paragraph:

Enzyme-linked ~~immunosorbant~~ immunosorbent assays. At various time periods pre- and post-immunization (or pre- and post- infection), mice from each group are bled, and individual mouse serum is tested using standard ~~quatitative~~ quantitative enzyme-linked ~~immunosorbant~~ immunosorbent assays (ELISA) to assess anti-HA or -NP specific IgG levels in the serum. IgG1 and IgG2a levels may optionally be tested, which are known to correlate with Th2 and Th1-type antibody responses, respectively. Briefly, sucrose gradient-purified A/PR/8/34 influenza virus is disrupted in flu lysis buffer (0.05 M Tris-HCL (pH 7.5-7.8), 0.5% ~~TritonX-100~~ Triton X-100, 0.6 M KCl) for 5 minutes at room temperature. Ninety-six well ELISA plates (Corning, Corning, NY) are coated with 200 HAU influenza in carbonate buffer (0.8 g Na_2CO_3, 1.47 g $NaHCO_3$, 500 ml ddH_20, pH to 9.6) and incubated overnight 4°C. Plates are blocked with 200 µl of 1% BSA in PBS for 1 hour at 37°C and washed 5 times with

PBS/0.025% Tween-20. Samples and standards are diluted in Standard Dilution Buffer (SDB) (0.5% BSA in PBS), added to microtiter plates at 50 µl per well, and incubated at 37°C for 90 min. Following binding of antibody, plates are washed 5 times. Fifty microliters of HRP-labeled goat anti-mouse Ig subtype antibody (Southern Biotechnology Associates) is then added at optimized concentrations in SDB, and plates are incubated for 1 hour at 37°C. After washing plates 5 times, 100 µl of ABTS substrate (10 ml 0.05 M Citrate (pH 4.0), ~~5 ul~~ 5 µl 30% H_2O_2, ~~50 ul~~ 50 µl 40 mM ABTS is added. Color is allowed to develop at room temperature for 30 min., and the reaction is stopped by adding 10 µl of 10% SDS. Plates are read at $O.D._{405}$. Data are analyzed using Softmax Pro Version 2.21 computer software (Molecular Devices, Sunnyvale, CA).

Please replace the paragraph at page 100, lines 1-8, with the following amended paragraph:

The circumsporozoite protein (CSP) is a target of ~~this pre-erythocytic~~ pre-erythrocytic immunity ~~(Hoffman *et al. Science* 252: 520 (1991)~~ (Hoffman *et al., Science* 252: 520 (1991)). In the *Plasmodium yoelii* (*P. yoelii*) rodent model system, passive transfer *P. yoelii* CSP-specific monoclonal antibodies (Charoenvit *et al., J. Immunol.* 146: 1020 (1991)), as well as adoptive transfer of *P. yoelii* CSP-specific $CD8^+$ T cells (Rodrigues *et al., Int. Immunol.* 3: 579 (1991), Weiss *et al., J. Immunol.* 149: 2103 (1992)) and $CD4^+$ T cells ~~(Renia *et al.* J Immunol. 150:1471 (1993))~~ (Renia *et al., J. Immunol.* 150:1471 (1993)) are protective. Numerous vaccines designed to protect mice against sporozoites by inducing immune responses against the *P. yoelii* CSP have been evaluated.

Please replace the paragraph at page 102, lines 17-26, with the following amended paragraph:

Infection and challenge. For a lethal challenge dose, the ID_{50} of *P. yoelli* sporozoites must be determined prior to experimental challenge. However, for example, it is also initially possible to inject mice intravenously in the tail vein with a dose of about 50 to 100 *P. yoelii* sporozoites (~~nonlethel~~ non-lethal, strain 17XNL). Forty-two hours after intravenous inoculation, mice are sacrificed and livers are removed. Single cell suspensions of hepatocytes in medium are prepared, and $2x10^5$ hepatocytes are placed into each of 10 wells of a multi-chamber slide. Slides may be dried and frozen at -70^0C until analysis. To count the number of schizonts, slides are dried and incubated with NYLS1 before incubating with FITC-labeled goat anti-mouse Ig, and the numbers of liver-stage schizonts in each chamber are counted using fluorescence microscopy.

Please replace the paragraph at page 102, lines 27-30, with the following amended paragraph:

Once it is demonstrated that castration and/or immunization reduces the numbers of infected hepatocytes, blood smears are obtained to determine if immunization ~~protect~~ protects against blood stage infection. Mice can be considered protected if no parasites are found in the blood smears at days 5-14 days post-challenge.

Please replace the paragraph at page 103, lines 9-11, with the following amended paragraph:

Tuberculosis (TB) is a chronic infectious disease of the lung caused by the pathogen *Mycobacterium tuberculosis*, and is one of the most clinically significant infections worldwide. (see, *e.g.*, U.S.P.N. 5,736,524; for review see Bloom and Murray, 1993, Science 257, ~~1055~~ 1055).

Please replace the paragraph at page 105, lines 6-8, with the following amended paragraph:

Plasmid DNA. Suitable Ag85-encoding DNA sequences and vectors have been described previously. See, *e.g.*, U.S.P.N. 5,736,524. Other suitable expression vectors would be readily ascertainably by ~~hose~~ those skilled in the art.

Please replace the paragraph at page 105, lines 24-28, with the following amended paragraph:

Enzyme-linked ~~immunosorbant~~ immunosorbent assays. At various time periods pre- and post-immunization, mice from each group are bled, and individual mouse serum is tested using standard quantitative ELISA to assess anti-Ag85 specific IgG levels in the serum. IgG1 and IgG2a levels may optionally be tested, which are known to correlate with Th2 and Th-type antibody responses, respectively.

Please replace the paragraph at page 109, lines 17-22, with the following amended paragraph:

Any of the RevM10 gene transfer vectors known and described in the art may be used. For example, the retroviral RevM10 vector, pLJ-RevM10 is used to ~~transducer~~ transduce the HSC. The pLJ-RevM10 vector has been shown to enhance T cell engraftment after delivery into HIV-infected individuals (Ranga *et al., Proc. Natl. Acad. Sci. USA* 95:1201 (1998). Other methods of construction and retroviral vectors suitable for the preparation of GM HSC are well known in the art (see, *e.g.*, Bonyhadi *et al., J. Virol.* 71:4707 (1997)).

Please replace the paragraph at page 111, lines 20-25, with the following amended paragraph:

In this example, human cord blood (CB) HSC are collected and processed using techniques well known to those skilled in the art (see, *e.g.*, DiGusto *et al.*, *Blood*, 87:1261 (1997), Bonyhadi *et al.*, *J. Virol.* 71:4707 (1997)). A portion of each CB sample is HLA ~~phonotyped~~ phenotyped, and the $CD34^+$ donor cells are purified from the donor blood (or bone marrow), such as by using a flow cytometer or immunomagnetic beading, essentially as described above. Donor-derived HSC are identified by flow cytometry as being $CD34^+$.

Please replace the paragraph at page 112, lines 10-12, with the following amended paragraph:

In this example, $CD34^+$-enriched HSC undergo transfection by a linearized RevM10 plasmid utilizing particle-mediated ~~("gene gun" transfer)~~ ("gene gun") transfer essentially as described in Woffendin *et al.*, *Proc. Natl. Acad. Sci. USA*, 93:2889 (1996).